

Supplemental Data

Follow-Up Characteristics by Diagnosis.

Table S1. Follow-up characteristics for MS and NMOSD patients.

| | MS N=907 | | NMOSD N=77 | | p-value^a |
|-----------------------------------------------|--------------------------|----------------|-------------------------|----------------|----------------------------|
| Follow Up Characteristics | N or Mean | SD or % | N or Mean | SD or % | |
| Cumulative rituximab Dose (mg) | 3,713 (median=3,000) | 3015 | 7,526 (median=6,000) | 6,272 | <0.001 |
| Patients who switched to ocrelizumab | 169 | 18.9% | 0 | 0.0% | - |
| Cumulative ocrelizumab dose (mg)* | 1,141 (median= 1,200) | 414 | - | - | - |
| Time on rituximab/ocrelizumab (months) | 29.7 | 21.0 | 47.2 | 40.0 | <0.001 |

Bold p-values indicate $p > 0.05$ and are considered statistically significant.

*Calculated of those who switched to ocrelizumab

^aComparing MS and NMOSD patients

Baseline Characteristics by Study Center

Table S2. Baseline characteristics by study center.

| | RMMSC N=725 | | NYUMSCC N=275 | | p-value ^a |
|-------------------------------------|----------------|---------|------------------|---------|----------------------|
| Baseline Characteristics | N or Mean | SD or % | N or Mean | SD or % | |
| Age (Years, SD) | 44.3 | 12.4 | 39.3 | 12.5 | <0.001 |
| Gender – Female | 496 | 68.4% | 191 | 69.5% | 0.751 |
| Race | | | | | <0.001 |
| White | 560 | 77.2% | 118 | 42.9% | |
| Black | 57 | 7.9% | 82 | 29.8% | |
| Other | 57 | 7.9% | 60 | 21.8% | |
| Unknown | 51 | 7.0% | 15 | 5.5% | |
| Ethnicity | | | | | <0.001 |
| Hispanic | 64 | 8.8% | 43 | 15.6% | |
| Non-Hispanic | 604 | 83.3% | 185 | 67.3% | |
| Unknown | 57 | 7.9% | 47 | 17.1% | |
| Smoking Status | | | | | 0.029 |
| Current Smoker | 106 | 14.6% | 25 | 9.2% | |
| Former Smoker | 199 | 27.5% | 67 | 24.7% | |
| Never Smoker | 420 | 57.9% | 179 | 66.1% | |
| Body Mass Index | 26.8 | 6.5 | 26.9 | 6.4 | 0.928 |
| Disability | | | | | 0.019 |
| No walking device needed | 438 | 60.4% | 188 | 69.9% | |
| Unilateral support (Cane) | 105 | 14.5% | 22 | 8.2% | |
| Bilateral support (Walker) | 77 | 10.6% | 27 | 10.4% | |
| Wheelchair | 105 | 14.5% | 32 | 11.9% | |
| Diagnosis | | | | | <0.001 |
| Relapsing-Remitting MS | 426 | 58.8% | 147 | 53.5% | |
| Secondary Progressive MS | 176 | 24.3% | 39 | 14.2% | |
| Primary Progressive MS | 98 | 13.5% | 21 | 7.6% | |
| NMOSD | 23 | 3.2% | 54 | 19.6% | |
| Other | 2 | 0.3% | 14 | 5.1% | |
| Disease Duration | 9.2 | 8.7 | 6.6 | 6.5 | <0.001 |
| Last DMT Used | | | | | <0.001 |
| Azathioprine | 2 | 0.3% | 13 | 4.7% | |
| Dimethyl fumarate | 106 | 14.6% | 47 | 17.1% | |
| Fingolimod | 127 | 17.5% | 28 | 10.2% | |
| Glatiramer Acetate | 82 | 11.3% | 18 | 6.5% | |
| Interferon | 56 | 7.7% | 10 | 3.6% | |
| Mycophenolate mofetil | 0 | 0.0% | 10 | 3.6% | |
| Natalizumab | 210 | 29.0% | 68 | 24.7% | |
| None | 102 | 14.1% | 61 | 22.2% | |
| Other/Missing | 29 | 0.4% | 16 | 5.8% | |
| Teriflunomide | 11 | 1.5% | 4 | 1.5% | |
| Time Since Last DMT (Months) | 7.8 | 19.8 | 5.5 | 20.6 | 0.171 |

Bold p-values indicate $p > 0.05$ and are considered statistically significant. RMMSC: Rocky Mountain Multiple Sclerosis Clinic; NYUMSCC: New York University Multiple Sclerosis Care Center; N: number; SD: standard deviation; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; DMT: disease modifying therapy.

^aComparing RMMSC and NYUMSCC patients

Table S3. Percentage of patients who experienced a serious safety event on rituximab/ocrelizumab by study center.

| | Total N (%) | Diagnosis | | p-value ^a |
|----------------------------------------------------|----------------|----------------|------------------|----------------------|
| | | RMMSC N (%) | NYUMSCC N (%) | |
| Infections resulting in: | 100 (8.6%)* | 85 (9.7%) | 15 (5.5%) | 0.019 |
| Hospitalization | 79 (6.5%)* | 70 (7.7%) | 9 (3.3%) | 0.012 |
| IV antibiotics (without hospitalization) | 6 (0.6%) | 6 (0.8%) | 0 (0.0%) | 0.196 |
| Extended dosing antibiotics | 15 (1.5%) | 9 (1.2%) | 6 (2.2%) | 0.260 |
| Infusion reaction requiring hospitalization | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Malignant Cancer | 9 (0.9%) | 8 (1.1%) | 1 (0.4%) | 0.458 |
| New autoimmune disease diagnosis | 6 (0.6%) | 3 (0.4%) | 3 (1.1%) | 0.355 |
| Thromboembolic event (Non-superficial) | 8 (0.8%) | 6 (0.8%) | 2 (0.7%) | 0.372 |
| Lymphopenia | | | | |
| <500 cells/mm3 | 48 (5.1%) | 29 (4.3%) | 19 (7.4%) | 0.056 |
| <200 cells/mm3 | 2 (0.2%) | 1 (0.1%) | 1 (0.4%) | 0.476 |
| Neutropenia | | | | |
| <1000 cells/mm3 | 14 (1.5%) | 9 (1.3%) | 5 (2.0%) | 0.483 |
| <500 cells/mm3 | 11 (1.2%) | 8 (1.2%) | 3 (1.2%) | 1.000 |
| Low IgG Values | | | | |
| <500 mg/dL | 38 (5.2%) | 30 (5.4%) | 8 (4.3%) | 0.545 |
| <300 mg/dL | 8 (1.1%) | 3 (0.5%) | 5 (2.6%) | 0.023 |
| Mortality | 14 (1.4%) | 12 (1.7%) | 2 (0.7%) | 0.372 |

Bold p-values indicate $p > 0.05$ and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event; RMMSC: Rocky Mountain Multiple Sclerosis Center; NYUMSCC: New York University Multiple Sclerosis Care Center

* Sixty-five patients were hospitalized a total of 79 times. Nine patients were hospitalized multiple times due to infections.

^aComparing RMMSC and NYUMSCC patients

Table S4. Follow-up characteristics by study center.

| Follow-Up Characteristics | RMMSC N=725 | | NYUMSCC N=275 | | p-value ^a |
|-----------------------------------------------|--------------------------|---------|--------------------------|---------|----------------------|
| | N or Mean | SD or % | N or Mean | SD or % | |
| Cumulative rituximab dose (mg) | 3,152 (median=2,500) | 2,261 | 6,410 (median=5,000) | 4,984 | <0.001 |
| Patients who switched to ocrelizumab | 131 | 18.1% | 38 | 13.8% | 0.109 |
| Cumulative ocrelizumab dose (mg)* | 1,191 (median= 1,200) | 413 | 971 (median= 1,200) | 378 | 0.004 |
| Cumulative anti-CD20 dose | 3,368 (median= 2,700) | 2,287 | 6,551 (median= 5,000) | 4,947 | <0.001 |
| Time on rituximab/ocrelizumab (months) | 28.7 (median=23) | 21.5 | 37.6 (median=29) | 27.1 | <0.001 |

Bold p-values indicate $p > 0.05$ and are considered statistically significant. RMMSC: Rocky Mountain Multiple Sclerosis Clinic; NYUMSCC: New York University Multiple Sclerosis Care Center

*Calculated of those who switched to ocrelizumab

^aComparing RMMSC and NYUMSCC patients

Types of Infections

Table S5. Number of infections resulting in hospitalizations, IV antibiotics (without hospitalization) and extended dosing antibiotics.

| | Hospitalization* n=65 (6.5% of patients) | IV Antibiotics (without Hospitalization) n=6 (0.6% of patients) | Extended Dosing Antibiotics n=15 (1.5% of patients) |
|-------------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------|
| Infection | N | N | N |
| Urinary Tract Infection | 35 | 2 | 10 |
| Sepsis | 22 | - | - |
| Pneumonia | 20 | - | 1 |
| Cellulitis | 5 | 1 | - |
| Abscess | 3 | - | - |
| C. Diff. Colitis | 2 | - | - |
| Kidney infection | 2 | - | - |
| Appendicitis | 2 | - | - |
| Influenza | 1 | - | - |
| Respiratory syncytial virus | 1 | - | - |
| Sinusitis / Bronchitis | 1 | 1 | - |
| Non-specific fever | 1 | - | -- |
| Wound infection | 2 | 1 | - |
| Stomach infection | 1 | - | - |
| Bacteremia | 1 | - | 1 |
| Hep B reactivation | 1 | -- | - |
| Pulmonary aspergillosis | 1 | - | - |
| Osteomyelitis | 1 | - | 1 |
| Viral pleural & pericardial effusion | 1 | - | - |
| Skin and joint infection | - | 1 | 1 |
| Bacterial Vaginosis | - | - | 1 |

*Some patients may have had multiple infections resulting in hospitalization

Association between Hypogammaglobulinemia and Infections

Table S6. Descriptive statistics and odds ratio for patients experiencing first infection who had an IgG value <500 mg/dL at any time compared to those with IgG values always ≥500 mg/dL

| <u>Infections resulting in Hospitalization Only*</u> | | | |
|-------------------------------------------------------------|-----------------------------------------|---------------------|--------------|
| | Infections (Hospitalization) | No Infection | Total |
| IgG Value: <500 mg/dL | 8 (21.1%) | 30 (78.9%) | 38 |
| IgG Value: Always ≥500 mg/dL | 40 (5.7%) | 660 (94.3%) | 700 |

*Chi-square test **p-value: 0.002**

| <u>Logistic Regression Analysis</u> | | | |
|--------------------------------------------|----------|--------------------------------|------------------|
| | N | Odds Ratio (95% CI) | p-value |
| Unadjusted Logistic Regression | 738 | 4.40 (1.89, 10.22) | <0.001 |
| Adjusted Logistic Regression* | 646 | 3.29 (1.13, 9.58) | 0.029 |

Infections resulting in Hospitalization, Extended Dosing Antibiotics or IV Antibiotics^

| | All Infections | No Infection | Total |
|-------------------------------------|-----------------------|---------------------|--------------|
| IgG Value: <500 mg/dL | 9 (23.7%) | 29 (76.3%) | 38 |
| IgG Value: Always ≥500 mg/dL | 52 (7.4%) | 648 (92.6%) | 700 |

^ Chi-square test **p-value: 0.004**

| <u>Logistic Regression Analysis</u> | | | |
|--------------------------------------------|----------|--------------------------------|----------------|
| | N | Odds Ratio (95% CI) | p-value |
| Unadjusted Logistic Regression | 738 | 3.87 (1.74, 8.60) | 0.002 |
| Adjusted Logistic Regression* | 646 | 3.15 (1.16, 8.55) | 0.024 |

Note: Lab value<500 mg/dL at least once at any time, not necessarily at time of infection

Bold p-values indicate p>0.05 and are considered statistically significant.

*Adjusting for age at first infusion, gender, disease duration, diagnosis (Relapsing MS, Progressive MS or Other), and disability at baseline

Association between Lymphopenia and Infections

Table S7. Descriptive statistics and odds ratio for patients experiencing first infection who had lymphopenia at any time compared to those without.

| <u>Infections resulting in Hospitalization Only*</u> | | | |
|-------------------------------------------------------------|-----------------------------------------|--------------------------------|----------------|
| | Infections (Hospitalization) | No Infection | Total |
| Lymphopenia <500 cells/mm³ | 8 (16.7%) | 40 (83.3%) | 48 |
| No Lymphopenia | 56 (6.3%) | 832 (93.7%) | 888 |
| *Chi-square test p-value: 0.013 | | | |
| Logistic Regression Analysis | | | |
| | N | Odds Ratio (95% CI) | p-value |
| Unadjusted Logistic Regression | 936 | 2.97 (1.33, 6.65) | 0.008 |
| Adjusted Logistic Regression* | 926 | 2.27 (0.93, 5.54) | 0.006 |

Infections resulting in Hospitalization, Extended Dosing Antibiotics or IV antibiotics^

| | All Infections | No Infection | Total |
|-------------------------------------------------|-----------------------|--------------------------------|----------------|
| Lymphopenia <500 cells/mm³ | 10 (20.8%) | 38 (79.2%) | 48 |
| No Lymphopenia | 69 (77.7%) | 819 (92.2%) | 888 |
| ^ Chi-square test p-value: 0.005 | | | |
| Logistic Regression Analysis | | | |
| | N | Odds Ratio (95% CI) | p-value |
| Unadjusted Logistic Regression | 936 | 3.12 (1.49, 6.53) | 0.003 |
| Adjusted Logistic Regression* | 926 | 2.55 (1.12, 5.81) | 0.012 |

Note: Lab value<500 mg/dL at least once at any time, not necessarily at time of infection

Bold p-values indicate p>0.05 and are considered statistically significant.

*Adjusting for age at first infusion, gender, disease duration, diagnosis (Relapsing MS, Progressive MS or Other), and disability at baseline

Characteristics of Patients who Experienced an SSE

Table S8. Baseline characteristics for those who experience an SSE and those who do not.

| | No SSE N=823 | | SSE* N=177 | | p-value[†] |
|-----------------------------------------|------------------------|----------------|----------------------|----------------|------------------------------|
| Baseline Characteristics | N or Mean | SD or % | N or Mean | SD or % | |
| Age (Years, SD) | 42.3 | 12.5 | 45.8 | 13.0 | 0.001^β |
| Gender – Female | 572 | 69.5% | 115 | 65.0% | 0.238 [†] |
| Race | | | | | 0.616 [†] |
| White | 553 | 67.2% | 125 | 70.6% | |
| Black | 116 | 14.1% | 23 | 13.0% | |
| Other | 96 | 11.7% | 21 | 11.9% | |
| Unknown | 58 | 7.1% | 8 | 4.5% | |
| Ethnicity | | | | | 0.267 [†] |
| Hispanic | 90 | 10.9% | 17 | 9.6% | |
| Non-Hispanic | 642 | 78.0% | 147 | 83.1% | |
| Unknown | 91 | 11.1% | 13 | 7.3% | |
| Smoking Status | | | | | 0.515 [†] |
| Current Smoker | 111 | 13.6% | 20 | 11.3% | |
| Former Smoker | 222 | 27.1% | 44 | 24.9% | |
| Never Smoker | 486 | 59.34% | 113 | 63.8% | |
| Body Mass Index | 27.1 | 6.6 | 25.8 | 6.0 | 0.022^β |
| Disability | | | | | <0.001[†] |
| No walking device needed | 548 | 67.1% | 78 | 44.1% | |
| Unilateral support (Cane) | 103 | 12.6% | 24 | 13.6% | |
| Bilateral support (Walker) | 81 | 9.9% | 23 | 13.0% | |
| Wheelchair | 85 | 10.4% | 52 | 29.4% | |
| Diagnosis | | | | | <0.001[†] |
| Relapsing-Remitting MS | 507 | 61.6% | 66 | 37.3% | |
| Secondary Progressive MS | 154 | 18.7% | 61 | 34.5% | |
| Primary Progressive MS | 101 | 12.3% | 18 | 10.2% | |
| NMOSD | 45 | 5.5% | 32 | 18.1% | |
| Other | 16 | 1.9% | 0 | 0.0% | |
| Disease Duration | 8.2 | 8.0 | 10.1 | 9.3 | 0.006^β |
| Last DMT Used | | | | | 0.102 [†] |
| Azathioprine | 10 | 1.2% | 5 | 2.8% | |
| Dimethyl fumarate | 128 | 15.6% | 25 | 14.1% | |
| Fingolimod | 130 | 15.8% | 25 | 14.1% | |
| Glatiramer Acetate | 86 | 10.5% | 14 | 7.9% | |
| Interferon | 54 | 6.6% | 5 | 7.9% | |
| Mycophenolate mofetil | 5 | 0.6% | 5 | 2.8% | |
| Natalizumab | 220 | 26.7% | 58 | 32.8% | |
| None | 140 | 17.0% | 23 | 13.0% | |
| Other/Missing | 37 | 4.5% | 8 | 4.5% | |
| Teriflunomide | 13 | 1.6% | 2 | 1.1% | |
| Time Since Last DMT (Months, SD) | 7.7 | 20.6 | 5.0 | 17.0 | 0.141 ^β |

Bold p-values indicate $p > 0.05$ and are considered statistically significant. SSE: serious safety event; N: number; SD: standard deviation; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; DMT: disease modifying therapy.

*includes infusion reaction resulting in hospitalization, new diagnosis of malignant cancer, new diagnosis of an autoimmune disease, thromboembolic event (non-superficial), lymphopenia (< 500 cells/mm³), neutropenia (< 1000 cells/mm³), IgG values (< 500 mg/dL), death or infections resulting in hospitalization, extended dosing antibiotics or IV antibiotics.

^α Comparing those with no SSE to those with an SSE

^β T-test

[†] Chi-squared tests

Table S9. Follow-up characteristics for those who experience an SSE and those who do not.

| Follow Up Characteristics | No SSEs N=823 | | SSE [^] N=177 | | p-value ^α |
|-----------------------------------------------|-------------------------|---------|---------------------------|---------|------------------------------|
| | N or Mean | SD or % | N or Mean | SD or % | |
| Cumulative rituximab Dose (mg) | 3,749 (median=3,000) | 3,262 | 5,215 (median=4,000) | 4,309 | <0.001^β |
| Patients who switched to ocrelizumab | 139 | 16.9% | 30 | 17.0% | 0.985 [†] |
| Cumulative ocrelizumab dose (mg)* | 1,137 (median=1,200) | 422 | 1,160 (median=1,200) | 384 | 0.788 ^β |
| Time on rituximab/ocrelizumab (months) | 28.8 (median=24) | 21.2 | 42.0 (median=32) | 29.7 | <0.001^β |

Bold p-values indicate $p > 0.05$ and are considered statistically significant. SSE: serious safety event; N: number; SD: standard deviation.

[^]Includes infusion reaction resulting in hospitalization, new diagnosis of malignant cancer, new diagnosis of an autoimmune disease, thromboembolic event (non-superficial), lymphopenia (< 500 cells/mm³), neutropenia (< 1000 cells/mm³), IgG values (< 500 mg/dL), death or infections resulting in hospitalization, extended dosing antibiotics or IV antibiotics.

*Calculated of those who switched to ocrelizumab

^α Comparing those with no SSE to those with an SSE

^β T-test

[†] Chi-squared tests

Table S10. Follow-up characteristics for those who experience an SSE by type at time of SSE.

| | First Serious Infection (N=86) | Cancer (N=9) | Autoimmune disease (N=6) | Thromboembolic event (N=8) |
|-----------------------------------------------|------------------------------------------|-------------------------------|------------------------------------|--------------------------------------|
| Follow Up Characteristics | N or Mean [SD or %] | N or Mean [SD or %] | N or Mean [SD or %] | N or Mean [SD or %] |
| Cumulative rituximab Dose (mg) | 3,705 [3,346] Median=2,500 | 3,167 [2,511] Median=4,000 | 4,667 [4,761] Median=3,000 | 3,643 [2,116] Median=3,000 |
| Patients who switched to ocrelizumab | 2 (2.3%) | 1 (11.1%) | 0 (0.0%) | 0 (0.0%) |
| Cumulative ocrelizumab dose (mg)* | 600 [.] Median=600 | 1,200 [.] Median=1,200 | . | . |
| Time on rituximab/ocrelizumab (months) | 25.1 [28.9] Median=19.0 | 38.8 (34.3) Median=50.0 | 19.0 (15.6) Median=16.5 | 31.5 [28.3] Median=27.0 |
| | Lymphopenia (N=48) | Neutropenia (N=14) | Low IgG Values (N=38) | Mortality (N=14) |
| Follow Up Characteristics | N or Mean [SD or %] | N or Mean [SD or %] | N or Mean [SD or %] | N or Mean [SD or %] |
| Cumulative rituximab Dose (mg) | 2,593 [2,408] Median=2,000 | 2,923 [1,801] Median=2,500 | 5,454 [4,812] Median=3,500 | 2,962 [1,738] Median= 2,500 |
| Patients who switched to ocrelizumab | 3 (6.3%) | 1 (7.1%) | 5 (13.2%) | 0 (0.0%) |
| Cumulative ocrelizumab dose (mg)* | 500 [173] Median=600 | 300 [.] Median=300 | 1140 [537] Median = 1200 | . |
| Time on rituximab/ocrelizumab (months) | 17.8 [20.6] Median=11.0 | 17.9 [13.3] Median=15.0 | 44.8 [32.8] Median=42.0 | 30.4 [21.6] Median= 28.0 |

*Calculated of those who switched to ocrelizumab

SSE: serious safety event; N: number; SD: standard deviation.

Subgroup Analysis- By Age

Table S11. Percentage of patients who experienced a serious safety event while on rituximab/ocrelizumab by age.

| | Total N (%) | Age | | p-value ^a |
|----------------------------------------------------|----------------|-----------------------------|-----------------------------|----------------------|
| | | <55 years N=808 N (%) | ≥55 years N=192 N (%) | |
| Infections resulting in: | | | | |
| Hospitalization | 79 (6.5%)* | 53 (5.3%)* | 26 (11.5%)* | 0.005 |
| IV antibiotics (without hospitalization) | 6 (0.6%) | 4 (0.5%) | 2 (1.0%) | 0.325 |
| Extended dosing antibiotics | 15 (1.5%) | 12 (1.5%) | 3 (1.6%) | 1.000 |
| Infusion reaction requiring hospitalization | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | - |
| Malignant Cancer | 9 (0.9%) | 6 (0.7%) | 3 (1.6%) | 0.386 |
| New autoimmune disease diagnosis | 6 (0.6%) | 5 (0.6%) | 1 (0.5%) | 1.000 |
| Thromboembolic event (Non-superficial) | 8 (0.8%) | 4 (0.5%) | 4 (2.1%) | 0.049 |
| Lymphopenia | | | | |
| <500 cells/mm3 | 48 (5.1%) | 29 (3.8%) | 19 (10.7%) | <0.001 |
| <200 cells/mm3 | 2 (0.2%) | 2 (0.3%) | 0 (0.0%) | 0.656 |
| Neutropenia | | | | |
| <1000 cells/mm3 | 14 (1.5%) | 11 (1.5%) | 3 (1.7%) | 0.736 |
| <500 cells/mm3 | 11 (1.2%) | 8 (1.1%) | 3 (1.7%) | 0.445 |
| Low IgG Values | | | | |
| <500 mg/dL | 38 (5.2%) | 28 (4.7%) | 10 (7.0%) | 0.256 |
| <300 mg/dL | 8 (1.1%) | 5 (0.8%) | 3 (2.1%) | 0.186 |
| Mortality | 14 (1.4%) | 10 (1.2%) | 4 (2.1%) | 0.323 |

Bold p-values indicate $p > 0.05$ and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event; RMMSC: Rocky Mountain Multiple Sclerosis Center; NYUMSCC: New York University Multiple Sclerosis Care Center

* Sixty-five patients (43 <55 years; 22 ≥55 years) were hospitalized a total of 79 times (53 <55 years; 26 ≥55 years).

^a Comparing those with <55 years to those ≥55 years

Nine patients (6 <55 years; 3 ≥55 years) were hospitalized multiple times due to infections.

Subgroup Analysis- By Disability

Table S12. Baseline characteristics by disability.

| | No Walking Device N=626 | | Unilateral Support N=127 | | Bilateral Support N=104 | | Wheelchair N=137 | |
|-------------------------------------|----------------------------|---------|-----------------------------|---------|----------------------------|---------|---------------------|---------|
| Baseline Characteristics | N or Mean | SD or % | N or Mean | SD or % | N or Mean | SD or % | N or Mean | SD or % |
| Age (Years, SD) | 39.8 | 12.3 | 46.5 | 11.6 | 49.3 | 11.8 | 48.9 | 10.6 |
| Gender – Female | 439 | 70.1 | 77 | 60.6 | 78 | 75.0 | 88 | 64.2% |
| Race | | | | | | | | |
| White | 426 | 68.1 | 90 | 70.9 | 69 | 66.4 | 89 | 65.0 |
| Black | 73 | 11.7 | 25 | 19.7 | 17 | 16.4 | 23 | 16.8 |
| Other | 82 | 13.1 | 7 | 5.5 | 10 | 9.6 | 17 | 12.4 |
| Unknown | 45 | 7.2 | 5 | 3.9 | 8 | 7.8 | 8 | 5.8 |
| Ethnicity | | | | | | | | |
| Hispanic | 72 | 11.5 | 12 | 9.5 | 10 | 9.6 | 11 | 8.0 |
| Non-Hispanic | 487 | 77.8 | 107 | 84.3 | 77 | 74.0 | 116 | 84.7 |
| Unknown | 67 | 10.7 | 8 | 6.3 | 17 | 16.4 | 10 | 7.3 |
| Smoking Status | | | | | | | | |
| Current Smoker | 78 | 12.5 | 23 | 18.1 | 12 | 11.5 | 18 | 13.2 |
| Former Smoker | 156 | 24.9 | 39 | 30.7 | 31 | 29.8 | 40 | 29.4 |
| Never Smoker | 392 | 62.6 | 65 | 51.2 | 61 | 58.7 | 78 | 57.4 |
| Body Mass Index | 26.9 | 6.2 | 28.2 | 7.4 | 27.7 | 6.5 | 25.0 | 6.5 |
| Diagnosis | | | | | | | | |
| Relapsing-Remitting MS | 480 | 76.7 | 51 | 40.2 | 24 | 23.1 | 17 | 12.4 |
| Secondary Progressive MS | 41 | 6.6 | 44 | 34.7 | 44 | 42.3 | 84 | 61.3 |
| Primary Progressive MS | 39 | 6.2 | 25 | 19.7 | 29 | 27.9 | 26 | 19.0 |
| NMOSD | 53 | 8.5 | 6 | 4.7 | 7 | 6.7 | 9 | 6.6 |
| Other | 13 | 2.1 | 1 | 0.8 | 0 | 0.0 | 1 | 0.7 |
| Disease Duration | 6.7 | 6.9 | 9.7 | 8.2 | 11.5 | 9.5 | 13.6 | 9.9 |
| Last DMT Used | | | | | | | | |
| Azathioprine | 8 | 1.33 | 1 | 0.0 | 3 | 2.9 | 2 | 1.5 |
| Dimethyl fumarate | 103 | 16.5 | 16 | 12.6 | 21 | 20.2 | 12 | 8.8 |
| Fingolimod | 92 | 14.7 | 29 | 22.8 | 18 | 17.3 | 16 | 11.7 |
| Glatiramer Acetate | 63 | 10.1 | 11 | 8.7 | 5 | 4.8 | 21 | 15.3 |
| Interferon | 31 | 5.0 | 11 | 8.7 | 11 | 10.6 | 13 | 9.5 |
| Mycophenolate mofetil | 5 | 0.8 | 0 | 0.0 | 2 | 1.9 | 3 | 2.2 |
| Natalizumab | 161 | 58.1 | 35 | 12.6 | 31 | 11.2 | 50 | 18.1 |
| None | 130 | 20.8 | 15 | 11.8 | 6 | 5.8 | 11 | 8.0 |
| Other/Missing | 27 | 4.3 | 6 | 4.7 | 5 | 4.8 | 6 | 4.4 |
| Teriflunomide | 6 | 1.0 | 4 | 3.2 | 2 | 1.9 | 3 | 2.2 |
| Time Since Last DMT (Months) | 6.2 | 16.0 | 8.2 | 18.1 | 5.2 | 9.0 | 12.8 | 35.0 |

RMMSC: Rocky Mountain Multiple Sclerosis Clinic; NYUMSCC: New York University Multiple Sclerosis Care Center; N: number; SD: standard deviation; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; DMT: disease modifying therapy.

Table S13. Percentage of patients who experienced a serious safety event while on rituximab/ocrelizumab by disability at baseline.

| | Total N (%) | Disability | | | | p-value ^a |
|----------------------------------------------------|----------------|------------------------------|-----------------------------------------|----------------------------------------|----------------------------------------|----------------------|
| | | No Device N= 626 N (%) | Unilateral Support N=127 N (%) | Bilateral Support N=104 N (%) | Wheelchair -Bound N=137 N (%) | |
| Infections resulting in: | | | | | | |
| Hospitalization | 79 (6.5%)* | 17 (2.7%)* | 10 (7.1%)* | 13 (9.6%)* | 39 (21.2%)* | <0.001 |
| IV antibiotics (without hospitalization) | 6 (0.6%) | 2 (0.3%) | 0 (0.0%) | 2 (1.9%) | 2 (1.5%) | 0.078 |
| Extended dosing antibiotics | 15 (1.5%) | 5 (0.8%) | 2 (1.6%) | 2 (1.9%) | 6 (4.4%) | 0.016 |
| Infusion reaction requiring hospitalization | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | - |
| Malignant Cancer | 9 (0.9%) | 4 (0.6%) | 0 (0.0%) | 1 (1.0%) | 4 (2.9%) | 0.066 |
| New autoimmune disease diagnosis | 6 (0.6%) | 5 (0.8%) | 0 (0.0%) | 0 (0.0%) | 1 (0.7%) | 0.916 |
| Thromboembolic event (Non-superficial) | 8 (0.8%) | 0 (0.0%) | 3 (2.4%) | 1 (1.0%) | 4 (2.9%) | 0.003 |
| Lymphopenia | | | | | | |
| <500 cells/mm3 | 48 (5.1%) | 23 (4.0%) | 10 (8.2%) | 5 (5.0%) | 10 (7.9%) | 0.098 |
| <200 cells/mm3 | 2 (0.2%) | 0 (0.0%) | 2 (1.6%) | 0 (0.0%) | 0 (0.0%) | 0.029 |
| Neutropenia | | | | | | |
| <1000 cells/mm3 | 14 (1.5%) | 9 (1.6%) | 2 (1.6%) | 2 (2.0%) | 1 (0.8%) | 0.888 |
| <500 cells/mm3 | 11 (1.2%) | 7 (1.2%) | 2 (1.6%) | 1 (1.0%) | 1 (0.8%) | 0.916 |
| Low IgG Values | | | | | | |
| <500 mg/dL | 38 (5.2%) | 18 (3.9%) | 7 (7.5%) | 7 (8.1%) | 6 (6.4%) | 0.175 |
| <300 mg/dL | 8 (1.1%) | 5 (1.1%) | 1 (1.1%) | 1 (1.2%) | 1 (1.1%) | 1.000 |
| Mortality | 14 (1.4%) | 2 (0.3%) | 0 (0.0%) | 3 (2.9%) | 9 (6.6%) | <0.001 |

Bold p-values indicate p>0.05 and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event.

* Sixty-five patients (17 no device; 9 unilateral support; 10 bilateral support; 29 wheelchair-bound) were hospitalized a total of 79 times (17 no device; 10 unilateral support; 13 bilateral support; 39 wheelchair-bound). Nine patients (0 no device; 1 unilateral support; 2 bilateral support; 6 wheelchair-bound) were hospitalized multiple times due to infections.

^a Comparing all disability levels; Significance indicates outcomes are dependent on disability level

Subgroup Analysis- By Immunosuppression/Chemotherapy History

Table S14. Percentage of patients who experienced a serious safety event on rituximab/ocrelizumab by immunosuppression/chemotherapy history.

| | Total N (%) | Immunosuppression/Chemotherapy History [^] | | | p-value ^α |
|----------------------------------------------------|----------------|--------------------------------------------------------|---------------------------------------|---------------------------------------|----------------------|
| | | No history N= 841 N (%) | Prior treatment N= 106 N (%) | Current treatment N=26 N (%) | |
| Infections resulting in: | | | | | |
| Hospitalization | 79 (6.5%)* | 52 (5.6%) | 25 (14.8%) | 2 (7.1%) | 0.001 |
| IV antibiotics (without hospitalization) | 6 (0.6%) | 4 (0.5%) | 2 (1.9%) | 0 (0.0%) | 0.278 |
| Extended dosing antibiotics | 15 (1.5%) | 11 (1.3%) | 4 (3.7%) | 0 (0.0%) | 0.135 |
| Infusion reaction requiring hospitalization | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | - |
| Malignant Cancer | 9 (0.9%) | 9 (1.1%) | 0 (0.0%) | 0 (0.0%) | 0.699 |
| New autoimmune disease diagnosis | 6 (0.6%) | 6 (0.6%) | 0 (0.0%) | 0 (0.0%) | 1.000 |
| Thromboembolic event (Non-superficial) | 8 (0.8%) | 4 (0.5%) | 2 (1.9%) | 2 (7.1%) | 0.005 |
| Lymphopenia | | | | | |
| <500 cells/mm3 | 48 (5.1%) | 31 (3.9%) | 11 (11.0%) | 5 (20.0%) | <0.001 |
| <200 cells/mm3 | 2 (0.2%) | 0 (0.0%) | 1 (1.0%) | 1 (4.0%) | 0.007 |
| Neutropenia | | | | | |
| <1000 cells/mm3 | 14 (1.5%) | 10 (1.3%) | 2 (2.0%) | 2 (8.0%) | 0.057 |
| <500 cells/mm3 | 11 (1.2%) | 8 (1.0%) | 2 (2.0%) | 1 (4.0%) | 0.122 |
| Low IgG Values | | | | | |
| <500 mg/dL | 38 (5.2%) | 26 (4.1%) | 10 (12.5%) | 2 (10.0%) | 0.006 |
| <300 mg/dL | 8 (1.1%) | 1 (0.16%) | 6 (7.5%) | 1 (5.0%) | <0.001 |
| Mortality | 14 (1.4%) | 13 (1.5%) | 1 (0.9%) | 0 (0.0%) | 1.000 |

Bold p-values indicate $p > 0.05$ and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event.

[^]Excluding MS therapies of natalizumab, dimethyl fumarate and fingolimod.

* Sixty-five patients (47 no history; 16 prior treatment; 2 current treatment) were hospitalized a total of 79 times (47 no history; 25 prior treatment; 2 current treatment). Nine patients (4 no history; 5 prior treatment; 0 current treatment) were hospitalized multiple times due to infections.

^α Comparing no, prior and current treatment; Significance indicates outcomes are dependent on immunosuppression/chemotherapy History